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Inhaled fluticasone propionate and adrenal effects in adult asthma: systematic review and meta-analysis

M. Masoli*, M. Weatherall#, S. Holt¶, P. Shirtcliffe* and R. Beasley*,+

ABSTRACT: The dose–response relationship of inhaled fluticasone propionate (FP) for adrenal suppression in adults with asthma is not clear.

The current authors carried out a systematic review and meta-analysis of placebo-controlled randomised dose–response studies of ⩾4 weeks' duration, which assessed the adrenal effects of FP by cosyntropin stimulation tests in adult asthma. The main outcome measure was the proportion of subjects with adrenal function below the lower limit of the normal range.

Five studies, with a total of 732 subjects with asthma, met the inclusion criteria. Data on daily doses >1,000 μg were limited to one study. The proportion of subjects with adrenal function below the lower limit of the normal range on placebo was 3.9%; for a 500-μg per day increase in FP dose the odds of an abnormality increased by 1.38 (95% confidence interval 1.01–1.59). The continuous secondary outcome measures showed an inverse linear relationship with the FP dose up to 2,000 μg·day^{-1}.

In conclusion, for routine prescribing within the established therapeutic dose–response range (50–500 μg·day^{-1}), fluticasone propionate has minimal effects on adrenal function. This conclusion is limited by the paucity of long-term studies of daily doses of fluticasone propionate >1,000 μg and by the considerable individual variability in the response.

KEYWORDS: Adrenal suppression, asthma, dose–response, fluticasone, meta-analysis

In recent years, one of the major advances in the understanding of the use of inhaled corticosteroids (ICS) in the management of asthma has been the determination of the dose–response relationship for efficacy. It has been demonstrated that for all major clinical outcome measures in adults with moderately severe asthma, the average dose required to achieve the maximum therapeutic response is ~500 μg·day^{-1} of fluticasone propionate (FP) [1, 2] or mometasone [3], and ~1,000 μg·day^{-1} of budesonide [4], beclomethasone dipropionate (BDP) [5] or triamcinolone [6].

In contrast to efficacy, the dose–response relationships of the systemic effects of ICS in adults with asthma are uncertain. Research has focused primarily on adrenal suppression, but studies have yielded conflicting results. Interpretation of studies has proven difficult, in part because some studies have not been placebo controlled [7, 8] and others have been of short duration [8]. In addition, many studies have reported single morning plasma cortisol measurements [9]. This is an insensitive and variable measure for detecting adrenal suppression [10, 11]. Other limitations have included the study of healthy volunteers rather than subjects with asthma [12] and studies in which subjects were not randomised to different doses, but were sequentially administered ICS in increasing doses [13]. These limitations are reflected in the conclusions of the most recent Cochrane meta-analyses [14, 15], which state that data on the effect of ICS on adrenal function are limited and that the clinical significance of the findings is unclear.

To further investigate this issue, the current authors have undertaken a meta-analysis of the dose–response relationship of inhaled FP on adrenal function in adult asthma. The primary outcome measure was the proportion of subjects with adrenal function below the lower limit of the normal range, rather than the mean change in cortisol levels, a measurement with which many doctors are unfamiliar. In this way an attempt was made to provide data to address the question ''What is the probability a patient with asthma may develop abnormal adrenal function with different doses of ICS (in this case FP)?'' This

AFFILIATIONS
*Medical Research Institute of New Zealand,
#Wellington School of Medicine & Health Sciences, and
¶P3 Research, Wellington, New Zealand.
+School of Medicine, University of Southampton, Southampton, UK.

CORRESPONDENCE
R. Beasley
Medical Research Institute of New Zealand
PO Box 10055
Wellington
New Zealand
Fax: 64 44729224
E-mail: Richard.Beasley@mrinz.ac.nz

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study was possible only with FP, owing to the inadequate number of studies with other ICS, including BDP and budesonide, which are widely used in clinical practice.

METHODS

Search strategy

Searches were conducted of Medline from January 1, 1966 to August 2003, of Embase from 1980 to August 2003 and of the Cochrane Controlled Trials Register, using the keywords ''FP'' and ''adrenal'' or ''HPA axis'' (hypothalamic–pituitary–adrenal axis). When limited to English, the total number of studies was 2,911. GlaxoSmithKline (Brentford, UK), the manufacturer of FP, was asked for details of all relevant studies; no additional studies were identified. The current authors wrote to the authors of two studies for additional information, but this was not forthcoming. No relevant studies published in other languages were found on Medline and Embase. Finally, the reference lists of relevant studies were examined, but these revealed no further studies. The search strategy as recommended by the Quality Of Reporting Of Meta-analyses (QUOROM) statement is shown in figure 1.

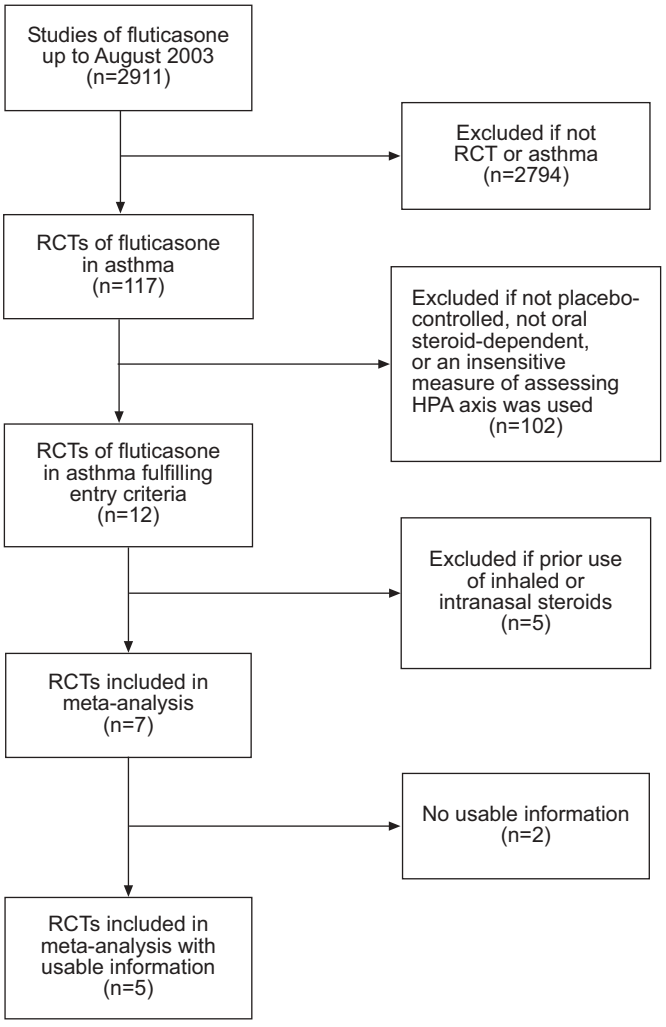

FIGURE 1. Process of inclusion of studies in the meta-analysis. RCT: randomised controlled trial; HPA: hypothalamic–pituitary–adrenal.

Inclusion criteria

Two of the current researchers examined each article's title and abstract, then the full article if necessary. To be included in this meta-analysis, a study had to meet the following criteria. It had to: 1) be a placebo-controlled, randomised trial of adolescents (aged >12 yrs) or adults with asthma; 2) use at least one dose of FP administered twice daily; 3) have a duration of $\geqslant$4 weeks; and 4) contain data on plasma cortisol response to cosyntropin stimulation. The stimulation test involved either 0.25 mg cosyntropin *i.v.* infusion over 6 h, with plasma cortisol concentration measured for $\geqslant$12 h after the start of the infusion, or 0.25 mg cosyntropin injected *i.m.* or *i.v.* with plasma cortisol concentration measured after 30–60 min. Both methods result in maximal acute stimulation of the adrenal gland [10, 11]. Studies in which participants were taking inhaled, intranasal or oral corticosteroids within 1 month of screening, or took concurrent intranasal corticosteroids during the study, were excluded because of the potential confounding effect on adrenal function.

Data extraction

The main analysis was based on the proportion of individuals with a response to cosyntropin stimulation below the lower limit of the normal range, referred to as ''abnormal adrenal function''. The primary outcome variable was the number of subjects with a peak plasma cortisol concentration of <18 $\mu g \cdot dL^{-1}$ or a rise in plasma cortisol concentration of <7 $\mu g \cdot dL^{-1}$ post-stimulation [10, 11]. The secondary outcome variables were the number of subjects with a peak plasma cortisol concentration of <18 $\mu g \cdot dL^{-1}$, the mean 8-h area under the concentration–time curve (AUC) for plasma cortisol, and the mean peak plasma cortisol concentration with cosyntropin stimulation. Standardised data were obtained from the study publications and the GlaxoSmithKline internal study reports. The data were extracted by two of the current researchers (M. Masoli and R. Beasley).

Data analysis

The main analysis was logistic regression modelling of whether the proportion of subjects with abnormal HPA-axis measurements was related to the dose of inhaled FP. Where appropriate, a general additive model was also used as an exploratory tool to assess whether there was any curvature in the relationship between the logit of the proportion of subjects with an abnormal test and the dose of FP. As values of ''zero'' are excluded from ordinary logistic regression, a sensitivity analysis was also undertaken in which ''one'' was added to each of the study-dose combinations where there were no participants with adrenal suppression. The proportion of subjects with abnormal baseline cortisol stimulation tests was available in only some of the studies and, when present, was not matched with the number of subjects with abnormal cortisol stimulation tests during treatment. As a result, it was not possible to use this information in the analysis of the dose–response relationship for inhaled FP and HPA function.

The current authors planned a meta-analysis to estimate the odds ratio for abnormality for doses of 500 $\mu g \cdot day^{-1}$ *versus* placebo and 1,000 $\mu g \cdot day^{-1}$ *versus* placebo, using an inverse variance weighting approach [16, 17]; however, insufficient data were available to perform this analysis.

TABLE 1 Summary of studies used in the meta-analysis

First author [ref.]	Subjects n	Duration weeks	FP doses μg·day^{-1}	Device	FEV_1 % pred (mean)	Age range (mean)	Baseline ICS usage	SST	6 h cosyntropin
KELLERMAN [19]	118	4	500, 1000, 1500, 2000, Pred 10 mg	MDI			0	N	Y
SORKNESS A [20]	112	4	200, 1000, Pred 10 mg	Diskhaler	>50 (87)	18–51 (29)	0	N	Y
SORKNESS B [20]	83	4	200, 500	Diskhaler	>50 (86)	19–51 (31)	0	N	Y
LI [21]	82	4	200, 500, Pred 10 mg	MDI	⩾50 (86)	18–55 (31)	0	N	Y
WASSERMAN [22]	331	12	100, 200, 500	Diskhaler	50–80	12–74 (29)	0	Y	N

FP: fluticasone propionate; FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroid; SST: short cosyntropin test; MDI: metered dose inhaler; Pred: prednisone.

For analysis of the mean 8-h AUC for plasma cortisol and the mean peak plasma cortisol concentration (Peak), the meta-analysis was a meta-regression technique using the inverse estimated variances at each dose in a weighted regression and consisted of calculating the correct estimate of the standard error of the regression estimates from the diagonal elements of the inverse of the weighted regression matrix [16]. For the plots of AUC and Peak, the confidence limits for the predicted responses were calculated according to the method of DRAPER and SMITH [18].

RESULTS

Five studies met the criteria for inclusion in this analysis (table 1) [19–22], of which two were published together [20]. In total, 732 adolescents and adults with asthma were included in the studies. The doses of FP ranged 100–2,000 μg·day^{-1}, with three studies including a prednisone treatment arm [19–21]. FP was administered *via* metered dose inhaler (MDI) in two studies [19, 21], and Diskhaler in three studies [20, 22]. The studies were of 4–12 weeks' duration. Four studies measured plasma cortisol in response to 6-h cosyntropin infusion and one study utilised the short cosyntropin test. Two further studies could not be included in the meta-analysis as the findings were published in abstract form only and data were not available in standardised form [23, 24]. Five studies were excluded in which subjects took either inhaled or intranasal corticosteroids at the time of recruitment or took concomitant intranasal corticosteroids during the period of the study [25–29]. There was one published study in which data were not in the required format [30], three studies in which adrenal function was assessed by urine cortisol assessment [28, 31, 32] and one study with a duration of 3 weeks [33].

Primary outcome variable: abnormal peak or change in cortisol level post-stimulation

The proportion of subjects with adrenal function below the lower limit of the normal range at the end of treatment is shown in table 2. In a simple linear logistic regression of the probability of abnormal adrenal function *versus* dose of FP, the coefficient relating the logit of the probability to dose had a value$\pm$SE of $6.49\times10^{-4}\pm3.20\times10^{-4}$ ($p=0.042$; fig. 2). This is moderate evidence of a linear relationship between inhaled FP dose and the logit of the probability of an abnormality, *i.e.* there is a curved relationship between the inhaled FP dose and the probability of an abnormality. This indicates that the risk ratio for developing an abnormality on adrenal function testing is constant between successive increased doses of FP (*e.g.* 500 μg *versus* placebo or 1,000 μg *versus* 500 μg). The predicted probabilities of an abnormality of adrenal function in relation to dose of FP are shown in table 3 and figure 2. The proportion of subjects with abnormal adrenal function on placebo was 3.9% (seven out of 180). For a 500-μg increase in the daily dose of FP, the odds of an abnormality increased by 1.38 (95% confidence interval (CI) 1.01–1.89).

To include all available data, a sensitivity analysis was undertaken in which any cell count of zero was increased to one. With this strategy, there was a decrease in the strength of the linear association between the FP dose and the logit of the probability of an abnormality. For a 500-μg increase in the daily dose of FP, the odds of an abnormality were 1.26 (95% CI 0.94–1.70).

Secondary outcome variables

Abnormal cortisol peak

In a simple linear logistic regression of the probability of abnormality of the peak cortisol level *versus* the inhaled FP dose, the coefficient relating the logit of the probability to dose had a value$\pm$SE of $1.49\times10^{-3}\pm3.69\times10^{-4}$ ($p<0.0001$; fig. 3). This suggests a linear relationship between the inhaled FP dose and the logit of the probability of an abnormality. The proportion of subjects with abnormal adrenal function on placebo was 0.6% (oen out of 180). For a 500-μg increase in the daily dose of FP, the odds of an abnormality increased by 2.10 (95% CI 1.46–3.02). The sensitivity analyses resulted in a decrease in the slope of the relationship between FP dose and the probability of an abnormality.

Mean AUC and peak cortisol analyses

Three studies contributed to the meta-regression of FP dose and the mean AUC and peak cortisol levels (table 4) [16, 20].

TABLE 2 Subjects with an abnormal adrenal response at end of treatment

First author [ref.]	Dose μg·day^{-1}	Subjects n	Abnormal cortisol peak# or change¶ post-stimulation	Abnormal cortisol peak# post-stimulation
KELLERMAN [19]	0	20	0 (0)	0 (0)
	500	21	0 (0)	0 (0)
	1000	20	2 (10.0)	2 (10.0)
	1500	19	3 (15.8)	3 (15.8)
	2000	17	2 (11.8)	2 (11.8)
	Pred	21	6 (28.6)	6 (28.6)
SORKNESS A [20]	0	30	0 (0)	0 (0)
	200	26	0 (0)	0 (0)
	1000	29	0 (0)	0 (0)
	Pred	27	4 (14.8)	3 (11.1)
SORKNESS B [20]	0	29	0 (0)	0 (0)
	200	26	0 (0)	0 (0)
	500	28	0 (0)	0 (0)
LI [21]	0	17	0 (0)	0 (0)
	200	21	0 (0)	0 (0)
	500	23	1 (4.3)	1 (4.3)
	Pred	21	3 (14.3)	3 (14.3)
WASSERMAN [22]	0	84	7 (8.3)	1 (1.2)
	100	80	5 (6.3)	2 (2.5)
	200	82	5 (6.1)	1 (1.2)
	500	85	9 (10.6)	4 (4.7)

Data are presented as n (%), unless otherwise stated. Pred: prednisone. #: <18 μg·dL^{-1}; ¶: <7 μg·dL^{-1}.

There was a significant linear decline in mean AUC with dose, with a slope coefficient -3.36×10^{-2} (95% CI -0.45×10^{-2}– -6.26×10^{-2}; fig. 4). There was a significant linear decline in mean peak cortisol with dose, with a slope coefficient of -4.7×10^{-4} (95% CI -0.3×10^{-4}– -9.2×10^{-4}; fig. 5). These analyses suggest that for both mean AUC and peak cortisol analyses, there was an inverse linear relationship between adrenal function and dose of FP.

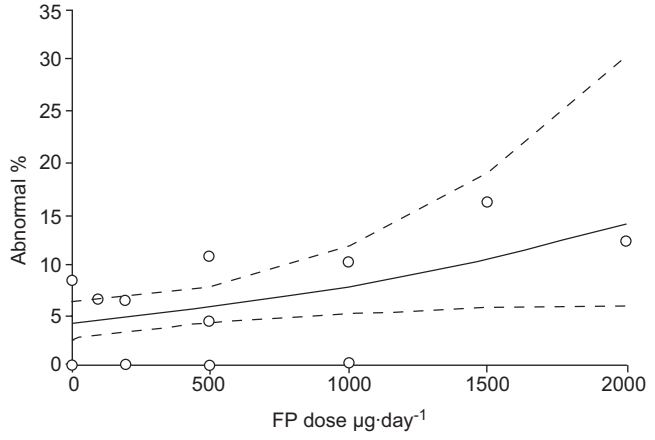

FIGURE 2. The raw percentages (○) and fitted logistic regression line (—) with 95% confidence limits (----) for the relationship between fluticasone propionate (FP) dose and probability of an abnormal cortisol stimulation test (peak cortisol <18 μg·dL^{-1} or change in cortisol <7 μg·dL^{-1}).

Comparison with prednisone 10 mg

Proportion of subjects taking prednisone 10 mg with abnormality

Three studies gave data for the proportion of subjects with an abnormality following treatment with 10 mg·day^{-1} of prednisone [19–21]. The pooled number of subjects with an abnormality (cortisol peak <18 μg·dL^{-1} or change <7 μg·dL^{-1} cortisol post-stimulation) was 13 out of 69 (18.8%; 95% CI 11.3–29.8%). By comparison, the estimate under the linear logistic model of dose–response relationship of the proportion abnormal on 2,000 μg·day^{-1} FP was 13.3% (95% CI 5.3–29.6%).

Continuous measures of adrenal function

The pooled estimate for mean AUC for the group taking 10 mg·day^{-1} prednisone, based on two studies [19, 20] was 136.4 μg·dL^{-1}·h (95% CI 128.6–144.1 μg·dL^{-1}·h). In comparison,

TABLE 3 Predicted probability of an abnormal adrenal response in relation to fluticasone propionate dose

Dose μg·day^{-1}	Predicted probability of an abnormality
0	3.9 (2.6–6.2)
500	5.5 (3.9–7.6)
1000	7.4 (4.7–11.4)
1500	10.0 (5.1–18.6)
2000	13.3 (5.3–29.6)

Data are presented as % (95% confidence interval), unless otherwise stated.

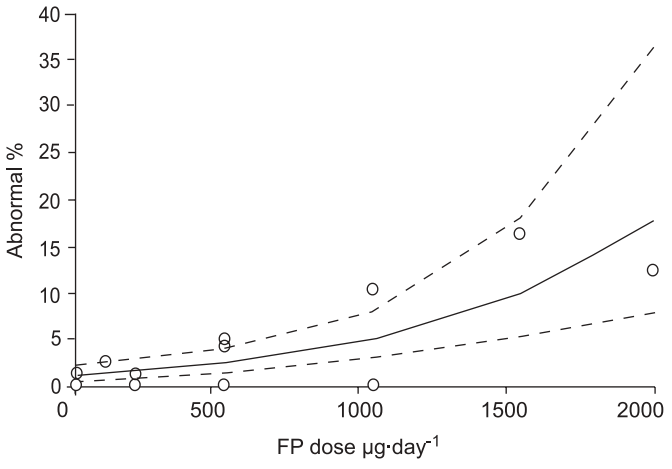

FIGURE 3. The raw percentages (○) and fitted logistic regression line (—) with 95% confidence limits (----) for the relationship between fluticasone propionate (FP) dose and the probability of an abnormal cortisol stimulation test (peak cortisol <18 μg·dL^{-1}).

the linear regression model predicts for 2,000 μg·day^{-1} FP a value of 145.5 μg·dL^{-1}·h (95% CI 98.8–192.1 μg·dL^{-1}·h).

The pooled estimate for peak cortisol for the group taking 10 mg·day^{-1} prednisone, based on two studies [19, 20] was 21.4 μg·dL^{-1} (95% CI 18.4–24.4 μg·dL^{-1}). In comparison, the linear regression model predicts for 2,000 μg·day^{-1} FP a value of 22.9 μg·dL^{-1} (95% CI 15.9–29.9 μg·dL^{-1}).

DISCUSSION

The major finding of this meta-analysis is that for all outcome variables examined, FP had minimal effects on adrenal function when prescribed within the therapeutic dose–response range of 50–500 μg·day^{-1} to adult subjects with asthma.

Methodological issues

Before discussing the results of this meta-analysis in detail, it is necessary to consider the major methodological issues relevant to its design. The first was the use of the proportion of subjects with adrenal function below the lower limit of the normal range as the main outcome variable. The reason for this novel approach was to address the question which doctors require in considering the use of ICS, namely ''What is the probability that my patient may develop abnormal adrenal function with different doses of ICS (in this case FP)?'' However, even with this approach, there is considerable uncertainty about the clinical significance of these criteria. This is illustrated by the finding that ~4% of subjects on placebo had abnormal adrenal function, reflecting the derivation of the ''normal values'' as encompassing 95% of the unaffected population. As a result, a measurement below the lower limit does not necessarily indicate that an individual has clinically significant adrenal suppression at risk of an adverse event in a stress situation. However, it does provide a useful method to assess the relative effect of different doses of ICS on adrenal function when comparison is made with placebo.

Another issue in relation to the assessment of adrenal function was the requirement for dynamic stimulation tests. Unfortunately, most studies have assessed morning cortisol levels. This is recognised as a screening test for adrenocortical excess but is an insensitive measure and poor predictor of adrenal suppression [11, 12]. In contrast, dynamic stimulation tests assess adrenal reserve and give an estimation of the capacity of the HPA axis to respond to stress. Measurement of urinary-free cortisol excretion is problematic owing to the inevitable compliance difficulties with urine collection, a lack of sensitivity and use of immunoassays that may be subject to interference produced by the metabolism of oral corticosteroids or ICS [34].

The duration of treatment with ICS therapy was another consideration. Although basal adrenal function can be easily

TABLE 4. Comparison of different methods of assessing adrenal function: subjects with an abnormal response *versus* mean area under the curve (AUC) and mean peak cortisol level post-stimulation

First author [ref.]	Doses μg·day^{-1}	Subjects n	Abnormal cortisol peak# or change¶ post-stimulation	Abnormal cortisol peak# post-stimulation	AUC μg·dL^{-1}·h	Peak μg·dL^{-1}
KELLERMAN [19]	0	20	0 (0)	0 (0)	198.2	30.3
	500	21	0 (0)	0 (0)	180.9	27.6
	1000	20	2 (10.0)	2 (10.0)	157.4	24.1
	1500	19	3 (15.8)	3 (15.8)	147.8	22.9
	2000	17	2 (11.8)	2 (11.8)	143.0	22.9
	Pred	21	6 (28.6)	6 (28.6)	124.0	19.7
SORKNESS A [20]	0	30	0 (0)	0 (0)	215.5±5.2	32.7±0.9
	200	26	0 (0)	0 (0)	224.4±4.8	33.7±0.7
	1000	29	0 (0)	0 (0)	207.2±6.2	30.6±0.9
	Pred	27	4 (14.8)	3 (11.1)	156.4±7.9	24.5±1.3
SORKNESS B [20]	0	29	0 (0)	0 (0)	202±5.5	31.1±1.0
	200	26	0 (0)	0 (0)	202.7±5.6	30.7±0.9
	500	28	0 (0)	0 (0)	202.3±7.0	30.3±1.1

Data are presented as n (%) or mean±SEM, unless otherwise stated. Pred: prednisone. #: <18 μg·dL^{-1}; ¶: <7 μg·dL^{-1}.

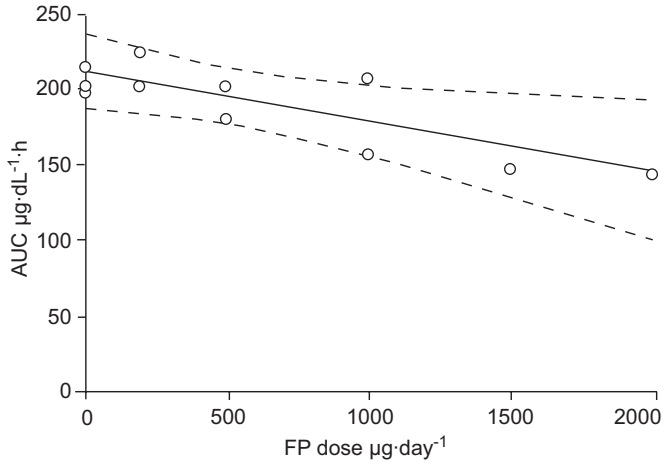

FIGURE 4. The plot of actual (○) and fitted linear regression (—) with 95% confidence limits (----) for the relationship between fluticasone propionate (FP) dose and area under the curve (AUC) for cortisol concentration.

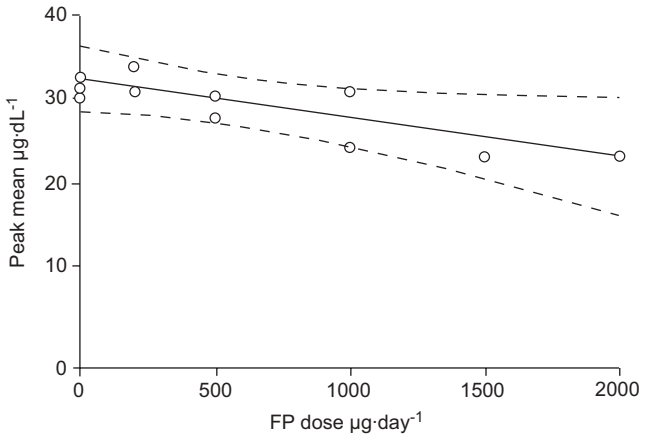

FIGURE 5. The plot of actual (○) and fitted linear regression (—) with 95% confidence limits (----) for the relationship between fluticasone propionate (FP) dose and peak mean cortisol concentration.

physiologically perturbed over hours to days by short-term administration of ICS, clinically significant suppression of the HPA axis with adrenocortical atrophy requires weeks or months of exogenous glucocorticoid exposure [35]. Studies were excluded if they were not of $\geqslant$4 weeks' duration, although even with this criterion, there were no studies of $\geqslant$3 months' duration. This is relevant because the risk of adrenal suppression is greater with increasing duration of high-dose ICS therapy [36].

It was necessary to exclude studies in which subjects used regular ICS therapy during the period prior to enrolment in the study, or concomitant use of intranasal corticosteroids during the study [15, 26–29]. The current authors also excluded studies in healthy nonasthmatic subjects due to the differential response in terms of adrenal suppression observed between asthmatic and nonasthmatic subjects [37, 38].

These stringent inclusion criteria markedly reduced the number of studies that were eligible for inclusion in the meta-analysis. Five studies with 732 subjects were included, with only one study which investigated doses >1,000 μg·day^{-1}. As a result, one of the conclusions of this meta-analysis is that there are insufficient data to determine confidently the long-term adrenal effects of FP in particular at doses >1,000 μg·day^{-1}. Further studies are required, including studies of novel dry-powder and hydrofluoroalkane-134a-containing MDIs, and studies in children, for which adequate data are currently unavailable [39].

Major findings

The major finding of this meta-analysis was that from a baseline proportion of subjects with abnormal adrenal function of ~4%, the odds ratio of an abnormality increased ~1.4-fold for each 500 μg·day^{-1} increase in FP dose. This means that with regular FP treatment at 500 μg·day^{-1}, the proportion of subjects with an abnormal adrenal function test increases from ~4% to 5.5%. The strength of the association decreased with the sensitivity analysis undertaken, to the extent that it was not statistically significant. In considering the clinical significance of these findings, the proportion of subjects with abnormal adrenal function tests in this study represents the proportion below the lower limits of the normal range derived to encompass 95% of the unaffected population, not necessarily those at risk of an adverse event due to clinically significant adrenal suppression. With the more conventional continuous measures of mean AUC and peak cortisol levels, a linear decline was observed with increasing FP doses of up to 2,000 μg·day^{-1}.

Inclusion of a treatment group taking 10 mg·day^{-1} in three of the studies allowed a comparison with FP for effects on adrenal function. An indirect comparison, based on the predicted effect of 2,000 μg·day^{-1} FP, suggests the effect on adrenal function of this FP dose was similar to that of 10 mg·day^{-1} oral prednisone, although the confidence intervals for the predictions were wide. This finding reinforces the importance of regularly reviewing patients on high doses of ICS and attempting to back-titrate the dose to within the therapeutic range.

Other systemic effects

The findings are consistent with the recent case–control studies of the dose–response of ICS and risk of both fractures and cataracts, based on the United Kingdom General Practice Research Database [40, 41]. These showed a gradual increase in risk of fracture with increasing doses of ICS, with a relative risk of 1.4 with 800–1,600 μg·day^{-1} BDP or equivalent, increasing to 1.9 at doses >1,600 μg·day^{-1} [40]. In terms of cataracts, an increased risk of 1.2 was observed at doses of 400–1,600 μg·day^{-1} BDP or equivalent, increasing further to 1.7 with doses >1,600 μg·day^{-1} [41]. These findings are broadly consistent with those observed with adrenal suppression in this meta-analysis in demonstrating a relatively flat dose–response up to at least 1,600 μg·day^{-1} BDP, equivalent to 800 μg·day^{-1} FP.

Therapeutic index

The present findings allow determination of a therapeutic ratio of efficacy/systemic adverse effects across a wide range of doses of inhaled fluticasone propionate in adult asthma. The current authors have previously shown that for most asthmatic

patients, 80–90% of the maximum therapeutic effect of fluticasone propionate can be obtained with doses ~200 μg·day^{-1}, with the maximum effect achieved at doses ~500 μg·day^{-1} [1, 2]. The similar determination of the dose–response of the adrenal effects of fluticasone propionate have shown that there is a small absolute risk to an individual receiving inhaled fluticasone propionate within this therapeutic range. However, with higher doses (not uncommonly used in clinical practice) [42], there is an increasing risk of adrenal suppression, despite minimal further efficacy, indicating a progressively worse therapeutic index. These conclusions are limited by the paucity of long-term studies investigating doses of fluticasone propionate >1,000 μg·day^{-1}, and the considerable individual variability in response to inhaled corticosteroids in asthma.

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